DETAILED ACTION

RCE Acknowledgment

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/22/2008 and 2/6/2009 has been entered.

2. Claims 65-105 are pending.

Claims 1-64 have been canceled.

Claims 102-105 have been newly added and are drawn to the elected invention.

Claims 67 and 81-85 are withdrawn from consideration for being drawn to a non-elected invention.

3. Claims 65-66, 68-80 and 86-105 including SEQ ID NO:1, 2 and 3 are examined in the present office action.

4. Rejections and objections not set forth below are withdrawn.

Specification

5. Figure 10 is objected to because it is blank. The brief description of the drawings describes Figure 10 but there is no corresponding Figure to match the description (see page 27 of the specification).

Claim Objection

6. Claims 65, 68 and 100-101 are objected to because 37 CFR 1.821(a-d) requires the use of the assigned sequence identifier (e.g. SEQ I.D. NO: X) in all instances where the description or claims of a patent application discuss sequences. The claims recite "amino acid sequence *YESP(K/R)*".

Full compliance with the sequence rules is required in response to this Office action. A complete response to this Office action must include both compliance with the sequence rules and a response to the issues set forth herein. Failure to fully comply with both of these requirements in the time period set forth in this Office action will be held to be non-responsive.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 65-66, 68-80 and 86-105 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection includes dependent claims.

In claim 65, it is unclear whether or not the "(SEQ ID NO:#)" is intended as a claim limitations. It is suggested that the parentheses be deleted and "of SEQ ID NO:#" be inserted in place of "(SEQ ID NO:#)" and "as shown in Figure #" also be deleted. All subsequent recitations in which a SEQ ID NO is set in parentheses are also rejected.

Claim 65 is indefinite for reciting "LpTFL1-like activity". Applicants have not defined this term. All subsequent recitations of "LpTFL1-like activity" are also rejected.

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 65-66, 68-80, 86 and 88-100 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of reducing or preventing flowering in a plant comprising expressing a polynucleotide comprising a nucleotide sequence having at least 83% identity with the coding sequence of SEQ ID NO:1 or 2 or with a nucleotide sequence encoding SEQ ID NO:3, wherein the nucleotide sequence encodes a polypeptide having LpTFL1-like activity and comprises the amino acid sequence YESP(K/R), or wherein the nucleotide sequence has any of the percent identities listed in claim 66.

Because of the indefiniteness of "LpTFL1-like activity" as discussed above, the Office interprets "LpTFL1-like activity" to mean any activity because Applicants do not define this term.

Applicants state "To isolate plant PEBP genes from ryegrass, a set of primers partially homologous to TFL1 of Arabidopsis, CEN of Antirrhinum, and a rice EST were designed" (page 29, 1st full paragraph). Applicants disclose that a 180 bp fragment was isolated by PCR which was subsequently used to isolate a cDNA that exhibited similarity to TFL1 and CEN, and was

named LpTFL1, whose sequence is set forth in SEQ ID NO:1. A genomic clone was isolated and the sequence is set forth in SEQ ID NO:2 (page 29, "Screening of cDNA and Genomic Library"). Applicants disclose that not all members of the PEBP gene family have the same activity in relation to floral control (page 3, lines 15-17).

Applicants do not identify essential regions of LpTFL1 protein encoded by SEQ ID NO:1 or 2, nor do Applicants describe any polynucleotide sequence that exhibits at least 83% identity to a nucleotide sequence encoding the polypeptide of SEQ ID NO:3 and wherein the encoded polypeptide has LpTFL1-like activity and comprises the amino acid sequence YESP(K/R).

The Federal Circuit has recently clarified the application of the written description requirement to inventions in the field of biotechnology. See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In summary, the court stated that a written description of an invention requires a precise definition, one that defines the structural features of the chemical genus that distinguishes it from other chemical structures. A definition by function does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. The court goes on to say, "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." *See University of California v. Eli Lilly and Co.*, 119 F.3d 1559; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Applicants fail to describe a representative number of polynucleotide sequences encoding a LpTFL1 protein of SEQ ID NO:3 falling within the scope of the claimed genus of

polynucleotides which exhibit at least 83% sequence identity to a nucleotide sequence encoding SEQ ID NO:3 and having LpTFL1-like activity and comprises the amino acid sequence YESP(K/R). Applicants only describe a single cDNA and genomic sequence of SEQ ID NO:1 and 2, respectively. Furthermore, Applicants fail to describe structural features common to members of the claimed genus of polynucleotides. Hence, Applicants fail to meet either prong of the two-prong test set forth by *Eli Lilly*. Furthermore, given the lack of description of the necessary elements essential for the LpTFL1 protein, it remains unclear what features identify a ryegrass LpTFL1 protein of SEQ ID NO:3. Since the genus of LpTFL1 proteins has not been described by specific structural features, the specification fails to provide an adequate written description to support the breath of the claims.

Applicant's arguments filed 12/22/2008 have been fully considered but they are not persuasive.

Applicants contend the specification highlights that the presence of the motif YESP(K/R) and in particular its serine residue, are believed to be important for the superior flowering repressor activity of LpTFL-1 (page 9 of Remarks, 4th paragraph). Thus, Applicants contend one skilled in the art would understand that the inventors were in possession of the claimed method. Applicants contend accession numbers listed in the Table filed with the amendment dated May 1, 2008 have been provided (page 10 of Remarks, 2nd paragraph). Applicants request that the Examiner consider the Declaration filed with the amendment dated May 1, 2008 (page 10 of Remarks, 3rd paragraph).

In the 1.132 Declaration filed May 1, 2008, Dr. Lenk states:

"The amended claim 1 defines the sequence (i) to show a sequence Identity of at least 83% to the specific nucleotide sequences defined in sections (a) and (b) of claim 1; (ii) by the fact that the

encoded polypeptide has LpTFLI-like activity; and (III) by the fact that the encoded polypeptide comprises the amino acid sequence YESP(K/R)" (page 2 of Declaration, 4th paragraph).

The Office contends Applicants have not defined "LpTFL1-like activity". In fact, the state-of-the-art teaches that not all TFL1 homologs have the same activity. Jensen et al (2001, Plant Physiology 125:1517-1528) states that TFL1 from *Arabidopsis* and its homolog CEN from *Antirrhinum* have been identified as a group of genes that specify an indeterminate identity of inflorescence meristems. Jensen et al teach that in addition to its effect on meristem fate, TFL1 also extends the vegetative phase of Arabidopsis, but CEN does not seem to have a flowering time role in *Antirrhinum* (page 1518, right column, 1st full paragraph). Therefore, it is not clear to what activity applicants are referring, as stated in the 112 2nd rejection. The Office contends the importance of the YESP(K/R) motif is questionable because TFL1 and CEN do not contain the YESP(K/R) motif and they are homologs of LpTFL1 (See page 1519, Panel B).

In the 1.132 Declaration filed May 1, 2008, Dr. Lenk attached a Table that lists genes homologous to LpTFL1 that are retrievable from public databases and Dr. Lenk indicates their sequence identities to LpTFL1. Dr. Lenk states

"All of the genes In the Table that have an identity of at least 83% on the nucleotide level encode an amino acid sequence having the motif YESP(K/R). From my experience, it Is reasonable to believe that one of skill in the art would recognize that these sequences will be useful for reducing or preventing flowering In plants by expressing them therein, as was shown in the patent application for LpTFL1" (page 2 of Declaration, 4th paragraph).

The Office contends the submitted Table is illegible and requests that it be submitted again. In addition, the Office contends that the IDS listing the specified accession numbers was not received and requests that it be resubmitted. Lastly, the Office contends Dr. Lenk has not provided any data that indicates the sequences listed in the Table would prevent or reduce flowering because no data has been provided linking the structure YESP(K/R) to a function of

reducing or preventing flowering. It is noted that TFL1 and CEN do not contain the YESP(K/R) motif and overexpressing TFL1 prevents or reduces flowering (page 1519, panel B and page 1520, left column, top paragraph).

Scope of Enablement

9. Claims 65-66, 68-80, 86, 88-100 and 102-105 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO:1 or 2 encoding SEQ ID NO:3 and plant transformation therewith and method of reducing or preventing flowering comprising expressing SEQ ID NO:1 or 2 or a polynucleotide encoding SEQ ID NO:3 in a plant, does not reasonably provide enablement for any polynucleotide exhibiting less than 100% sequence identity to SEQ ID NO:1 or 2 or to a polynucleotide encoding a protein exhibiting less than 100% identity to SEQ ID NO:3 and plant transformation therewith and method of reducing or preventing flowering comprising said polynucleotide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claimed invention is not supported by an enabling disclosure taking into account the *In re Wands* factors (858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). *In re Wands* lists a number of factors for determining whether or not undue experimentation would be required by one skilled in the art to make and/or use the invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior

art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claim.

The claims are drawn to a method of reducing or preventing flowering in a plant comprising expressing a polynucleotide comprising a nucleotide sequence having at least 83% identity with the coding sequence of SEQ ID NO:1 or 2 or with a nucleotide sequence encoding SEQ ID NO:3, wherein the nucleotide sequence encodes a polypeptide having LpTFL1-like activity and comprises the amino acid sequence YESP(K/R), or wherein the nucleotide sequence has any of the percent identities listed in claims 66 or 102.

Because of the indefiniteness of "LpTFL1-like activity" as discussed above, the Office interprets "LpTFL1-like activity" to mean any activity because Applicants do not define this term.

Applicants state "To isolate plant PEBP genes from ryegrass, a set of primers partially homologous to TFL1 of Arabidopsis, CEN of Antirrhinum, and a rice EST were designed" (page 29, 1st full paragraph). Applicants disclose that a 180 bp fragment was isolated by PCR which was subsequently used to isolate a cDNA that exhibited similarity to TFL1 and CEN, and was named LpTFL1, whose sequence is set forth in SEQ ID NO:1. A genomic clone was isolated and the sequence is set forth in SEQ ID NO:2 (page 29, "Screening of cDNA and Genomic Library"). Applicants disclose that not all members of the PEBP gene family have the same activity in relation to floral control (page 3, lines 15-17). Applicants disclose operably linking the ubiquitin promoter to the coding region of LpTFL1, and Arabidopsis transformation therewith (page 32, bottom paragraph). The transformed Arabidopsis plants exhibited a delay in flowering compared to wild type plants (*Ibid*). Applicants disclose that some of the transgenic

plants failed to produce flowers before they senescenced and died (page 33, top paragraph). Applicants disclose ryegrass transformed with said construct produced plants that exhibited a delayed flowering (page 43, top paragraph). Applicants disclose red fescue lines transformed with said LpTFL1 construct flowered at least two weeks later than the wild-type controls (page 51, bottom paragraph).

The state-of-the-art is such that one of skill in the art cannot predict which nucleic acids that exhibit less than 100% sequence identity to a nucleic acid encoding SEQ ID NO:3 will encode a protein with the same activity as a protein encoded by SEQ ID NO:1 or 2. The prediction of protein structure from sequence data and, in turn, utilizing predicted structural determinations to ascertain functional aspects of the protein, is extremely complex, and the positions within the protein's sequence where amino acid substitutions can be made with a reasonable expectation of maintaining function are limited (Bowie et al, Science 247:1306-1310, 1990, see especially page 1306). Proteins may be sensitive to alterations in even a single amino acid in a sequence. For example, the replacement of a glycine residue located within the START domain of either the PHABULOSA or PHAVOLUTA protein receptor with either an alanine or aspartic acid residue, alters the sterol/lipid binding domain (McConnell et al, Nature 411 (6838):709-713, 2001, see especially page 710, left column, 2nd paragraph).

Applicants disclose that even within the group of plant PEBP genes, there are gene members that do not produce the expected result. Applicants disclose that eleven amino acid residues in the plant PEBP sequences have so far been identified as essential for a functional protein (paragraph bridging pages 36 and 37). Applicants disclose that LpTFL1 differs from the consensus at one position (110), which is also the position with the highest degree of amino acid

variation between species. The members of the PEBP fall into three groups based on the amino acid at this position and not all members produce the same effect when transformed into a plant (page 37, top paragraph). Therefore, the Office contends that Applicants have not disclosed explicitly which amino acids are required to produce a polypeptide that when over expressed in a plant produces the claimed phenotype.

Given the specific amino acid sequence that is required for producing the claimed phenotype, Applicants have not disclosed how one makes or isolates any of the sequences that are encompassed by Applicants' broad claims. Applicants have not taught which regions of the respective polynucleotides can be used to amplify any of said polynucleotides or which regions can be used as a probe to isolate any of said polynucleotide sequences.

In the absence of guidance, undue trial and error experimentation would be required for one of ordinary skill in the art to screen through the multitude of non-exemplified sequences, either by using non-disclosed fragments of SEQ ID NO:1 or 2 as probes or by designing primers to undisclosed regions of SEQ ID NO:3 and isolating or amplifying fragments, subcloning the fragments, producing expression vectors and transforming plants therewith, in order to identify those, if any, that when over-expressed produce plants with a delayed flowering and wherein the.

Therefore, given the breadth of the claims; the lack of guidance and examples; the unpredictability in the art; and the state-of-the-art as discussed above, undue experimentation would be required to practice the claimed invention, and therefore the invention is not enabled.

Applicant's arguments filed 12/22/2008 and 2/6/2009 have been fully considered but they are not persuasive.

Applicants contend that the specification explicitly defines LpTFL1-like activity on page 4, lines 9-13 (paragraph bridging pages 10-11 of Remarks). Applicants state:

> "("Overexpression of LpTFL-1 in *Arabidopsis,* red rescue, and ryegrass results in a dramatic extension of the vegetative-inflorescence phase and a lateral branching in *Arabidopsis* that is consequently more extreme compared with overexpression of TFL1 in *Arabidopsis.* In addition, the results illustrate that LpTFL1 is capable of repressing flowering in perennial plants in the first year of growth and also in subsequent years.")"

The Office contends Applicants have not stated that the disclosed process of overexpressing LpTFL-1 resulting in the disclosed phenotype is the meaning of "LpTFL1-like activity". The specification does not explicitly define this term and it is not clear from the art what constitutes "LpTFL1-like activity". Even Jensen et al disclose that TFL1 and CEN have different activities (See page 1518, right column, 1st full paragraph where Jensen et al state "but CEN does not seem to have a flowering time role in *Antirrhinum.*")

Applicants contend the Examiner disregarded the disclosure in the specification on page 12, lines 5-9 describing the eleven essential amino acids in plant PEBP sequences and discussing how LpTFL1 relates to those sequences, and how the superior repressor activity of flowering is obtained (page 11 of Remarks, 1st full paragraph). Applicants contend the Examiner does not address why those eleven essential amino acids do not provide sufficient disclosure for one of skill in the art to be able to make and use the claimed invention without undue experimentation. Lastly, Applicants contend the Specification discloses how to: 1) make variants of the SEQ ID NOs... 2) calculate the percent identity between the SEQ ID NOs... and the variant sequence; and 3) test the variant sequence for functionality is a valid application of *binding* case law. Therefore, Applicants submit that *Ex parte Kubin* is on point (page 11 of Remarks, 2nd full paragraph).

The Examiner acknowledges the disclosure by Applicants of the eleven essential amino acids. The Office contends Applicants have not taught which other amino acids are required for the proper activity of the encoded polypeptide. Claim 65 as currently amended is directed toward a method comprising a nucleotide sequence having at least 83% identity with the nucleotide sequence of (a) or (b) and having LpTFL1-like activity. For the sake of this discussion, the Office will consider the recitation "LpTFL1-like activity" to be a certain quantifiable activity. The recitation of a nucleotide sequence having at least 83% identity represents a partial structure. That is, the encoded polypeptides share a certain percentage of structure with SEQ ID NO:3 while the remaining percentage of structure can vary. There is no teaching in the specification regarding which structure of the polypeptide can be varied while retaining the recited activity because guidance and working examples teaching unalterable structural and catalytic amino acid residues and amino acid residues tolerable to change is not provided by the specification. Further, there is no art-recognized correlation at the time of filing, between any structure, other than SEQ ID NO:3 of the instant application, and the recited activity. Consequently, there is no information about which amino acids can vary from SEQ ID NO:3 in the claimed genus of polypeptides and still retain the required activity.

In view of the broad scope of the claims, the specification's lack of specific guidance and additional working examples, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required, it would require undue experimentation for a skilled artisan to make and use the entire scope of the claimed invention. Therefore, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of

the claims must bear a reasonable correlation with the scope of enablement *(In re Fisher,* 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988).

The Office contends disclosing sequences that were known in the art at the time of filing that exhibit 83% identity to the nucleotide sequence of (a) or (b) and will produce plants that do not flower or have a reduced flowering when said sequence is transformed into a plant; wherein said sequences are disclosed in an IDS, will obviate the rejection.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

10. Claims 65-66, 68-72, 74, 86-93 are directed to non-statutory subject matter. This rejection is made because the claims are drawn to a method comprising expressing a polynucleotide comprising a nucleotide sequence or the coding sequence of a SEQ ID NO, which does not indicate that the "hand of man" was involved in the invention. Amending the claim to recite "an isolated nucleotide" or "an isolated coding sequence" will obviate the rejection.

11. Claims 65-66, 68-80 and 86-105 are deemed free of the prior art, given the failure of the prior art to teach or reasonably suggest a method of reducing or preventing flowering in a plant and a transgenic plant comprising an isolated polynucleotide of SEQ ID NO:1 or 2 encoding SEQ ID NO:3.

12. Claim 101 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stuart F. Baum whose telephone number is 571-272-0792. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached at 571-272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Stuart F. Baum/
Stuart F. Baum Ph.D.
Primary Examiner
Art Unit 1638
March 11, 2009